REMARKS

Claim 61 is pending in the subject application. By this Amendment, applicants have added new claim 66. Support for new claim 66 may be found in the specification *inter alia* at page 14, lines 14-15. Applicants maintain that new claim 66 raises no issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claim 61 and new claim 66 will be pending and under examination.

37 C.F.R. §1.72

The Examiner objected to the title of the invention under 37 C.F.R. §1.72 as allegedly not indicative of the claimed invention. In response, but without conceding the Examiner's ground of objection, applicants have amended the title of the invention as suggested by the Examiner. Accordingly, applicants maintain that the Examiner's ground of objection has been obviated and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Priority Claim

The Examiner indicated that a specific reference to the prior-filed applications to which priority is claimed as set forth in the original Declaration must be included in the first sentence of the specification in compliance with 37 C.F.R. §1.78(a). The Examiner further indicated that the status of the prior-filed applications must also be updated. In response, applicants have amended the first paragraph of the specification to reflect the priority data set forth in the original Declaration and the status of such applications. Accordingly, applicants maintain that the specification complies with the requirements of 37 C.F.R. §1.78 and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Rejection under 35 U.S.C. §102

The Examiner rejected claim 61 under 35 U.S.C. §102 as allegedly anticipated by Simmons et al. (1997). Specifically, the Examiner stated that one of the priority applications relied upon, i.e., U.S. Serial No. 08/831,823, filed April 2, 1997, does not provide support

for chemokine antagonists. Accordingly, the Examiner alleged that claim 61, as amended in the August 20, 2007 Amendment submitted in response to the October 17, 2006 Final Office Action, has an effective filing date of June 13, 1997 based upon the disclosure set forth in priority application U.S. Serial No. 08/876,078. The Examiner further alleged that Simmons et al. disclose a RANTES analogue that potently inhibited macrophage-tropic HIV-1 infection which anticipates the claimed invention.

In response, applicants respectfully traverse the Examiner's ground of rejection.

Applicants maintain that priority application U.S. Provisional Application No. 60/019,715, filed June 14, 1996 discloses CCR5 chemokine receptor antagonists and provides support for claim 61. For the Examiner's convenience, applicants attach hereto as Exhibit 1 a copy of U.S. Provisional Application No. 60/019,715. Applicants maintain that support for claim 61 may be found in the specification of U.S. Provisional Application No. 60/019,715 *inter alia* at page 11, lines 3-7; page 11, lines 29-31; page 29, lines 8-11; and page 19, lines 8-26 which disclose chemokine antagonists. Applicants note that page 19, lines 8-26 of U.S. Provisional Application No. 60/019,715 is verbatim to page 27, lines 4-21 of the instant application which applicant cited for support of the amendments made to claim 61 in the August 20, 2007 Amendment. Support for new claim 66 may be found in the specification of U.S. Provisional Application No. 60/019,715 *inter alia* at page 12, lines 6-7. Accordingly, applicants maintain that the claim 61 and new claim 66 are entitled to the filing date of U.S. Provisional Application No. 60/019,715, i.e. June 14, 1996. Thus applicants maintain that Simmons et al. (1997) is not a proper prior art reference under 35 U.S.C. §102.

In view of the remarks above, applicants maintain that the Examiner's ground of rejection under 35 U.S.C. §102 is not proper and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejections under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner stated that claim 61 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner alleged that the original application does not provide adequate support for the broadly claimed genus of antagonists that are capable of abrogating HIV-1 infection by binding to the CCR5 chemokine receptor. The Examiner stated that claim 61 does not limit the genus to any particular type of compound or any particular family of compounds. Specifically, the Examiner provided the following four rationales for this ground of rejection. First, the Examiner alleged that the disclosure fails to provide any significant structural information concerning the molecular determinants on CCR5 that modulate CCR5-CD4-gp120 events. Second, the Examiner alleged that the disclosure fails to provide adequate guidance pertaining to the structures of any particular subgenus of inhibitory agents. Third, the Examiner alleged that, although the specification provides a generic assay to identify potential candidate molecules, this assay fails to lead the skilled artisan to any particular subgenus of inhibitory agents. Fourth, the Examiner alleged that the state of the art as it pertains to HIV antiviral development is characterized by unpredictability.

In response, applicants respectfully traverse the Examiner's rejection. Applicants address below each of the Examiner's four rationales for this ground of rejection.

Applicants' Invention

Applicants' invention provides a method of inhibiting infection of a CD4+ cell by a macrophage-tropic HIV-1 which comprises contacting the

CD4+ cell with a CCR5 chemokine receptor antagonist which (a) binds to a CCR5 chemokine receptor on the surface of the CD4+ cell; (b) blocks fusion of HIV-1_{JR-FL} with a PM-1 cell; (c) does not block fusion of HIV-1_{BRU} with such PM-1 cell; and (d) does not activate an inflammatory response upon binding to the CCR5 chemokine receptor on the surface of the CD4+ cell; in an amount and under conditions such that fusion of the macrophage-tropic HIV-1 to the CD4+ cell is inhibited, so as to thereby inhibit infection of the CD4+ cell by the macrophage-tropic HIV-1. In addition, applicants' claimed invention provides that the CCR5 chemokine receptor antagonist may be a polypeptide.

Examiner's Rationale No.1

The Examiner alleged that the disclosure fails to provide any significant structural information concerning the molecular determinants on CCR5 that modulate CCR5-CD4-gp120 events.

Applicants maintain that, as disclosed in the application, and as recited in claim 61, the CCR5 chemokine receptor antagonist binds to a CCR5 chemokine receptor on the surface of a CD4+ cell and does not activate an inflammatory response upon binding to the CCR5 chemokine receptor on the surface of the CD4+ cell. The CCR5 chemokine receptor antagonist binds to the known CCR5 chemokine receptor for which endogenous chemokine ligands are known in the art in addition to those disclosed in the specification. Specifically, these are disclosed *inter alia* in the specification at page 1, line 32 to page 2, line 3; page 2, lines 28-34; page 7, lines 3-30; Figure 1; page 26, lines 8-18; page 34, lines 33-37; and page 35, Table 2a.

In addition to the ample description of the CCR5 chemokine receptor antagonists as recited in claim 61 and disclosed in the subject application, applicants maintain that one skilled in the art would readily understand a CCR5 chemokine receptor antagonist to be a compound which, upon binding to a chemokine receptor, namely, the CCR5 chemokine receptor, inhibits or blocks the receptor-mediated response activated by the binding to the receptor of its endogenous ligand(s).

Applicants maintain that the binding specificity of the CCR5 chemokine receptor antagonist to the CCR5 chemokine receptor disclosed in the subject application combined with the knowledge in the art regarding receptor antagonists provide sufficient guidance for one skilled in the art to understand the scope of the claimed genus of CCR5 chemokine receptor antagonist.

Applicants further maintain that the specification discloses the relationship between the physical/chemical properties and the function of the claimed CCR5 chemokine receptor antagonists. As explained starting on page 36, line 17, CCR5 (also known as C-C CKR-5) is the co-receptor, which, with CD4, is needed for HIV-1 entry into a cell. At page 36, lines 20-22, the specification states that "[i]t has been known for a decade that HIV-1 requires a second receptor for entry into CD4+ cells". As stated on page 36, lines 35-37, and as shown on page 37, Table 3, "[t]he expression of C-C CKR-5 on Hela-CD4 (human), COS-CD4 (simian) and 3T3-CD4 (murine) cells rendered each of them readily infectible by the primary, NSI strains ADA and BaL in the env-complementation assay of HIV-1 entry." Accordingly, applicants maintain that the specification discloses that HIV-1 requires two receptors for entry into a CD4+ cell, the second receptor being CCR5, and that the blocking of HIV-1 gp120 binding to CCR5 would inhibit entry of HIV-1 into a CD4+ cell. Thus, applicants maintain that one skilled in the art would understand the physical and chemical properties of the CCR5 chemokine receptor antagonists which enable them to bind to the CCR5 chemokine receptor on the surface of a CD4+ cell, and to block fusion of a CD4+ cell with a macrophage-tropic HIV-1, but not with a T-cell tropic HIV-1, which are particularly disclosed properties of such antagonists. Accordingly, applicants maintain that the specification clearly describes the correlation between the identifying properties and the function of the CCR5 chemokine receptor antagonist as recited in claim 61.

Examiner's Rationale No. 2

The Examiner alleged that the disclosure fails to provide adequate guidance pertaining to the structures of any particular subgenus of

inhibitory agents.

In response, applicants maintain that the now claimed genus of CCR5 chemokine receptor antagonists does not encompass all chemokine antagonists, but rather encompasses those which bind specifically to the CCR5 chemokine receptor on the surface of the CD4+ cell; block fusion of HIV-1_{JR-FL} with a PM-1 cell; do not block fusion of HIV-1_{BRU} with such PM-1 cell; and do not activate an inflammatory response upon binding to the CCR5 chemokine receptor on the surface of the CD4+ cell.

In addition, as the Examiner acknowledges on page 6 of the November 16, 2007 Office Action, multiple examples of CCR5 chemokine receptor antagonists are disclosed in the subject application. The specification discloses at page 12, CCR5-specific monoclonal antibodies, namely, 2D7, PA8, PA9, PA10, PA11, and PA12, as CCR5 chemokine receptor antagonists that inhibit infection of CD4+ cells by HIV-1. In addition, the disclosure beginning on page 26, line 29 and continuing to page 28, line 25, provides polypeptides which are chemokine derivatives that inhibit HIV-1 fusion, including N-terminal derivatives of RANTES, MIP1-α, MIP1-β, such as Met-RANTES, and N-terminal deletions of RANTES, MIP1-α, MIP1-β or MCP-1, such as the peptide having a deletion of 8 amino acids at the N-terminus of MCP-1. Such polypeptides form an exemplary subgenus of the now claimed genus of CCR5 chemokine receptor antagonists as now recited in new claim 66.

Applicants maintain that the knowledge in the art and the disclosure of the subject specification provide a more than adequate written description of the common physical and chemical properties of CCR5 chemokine receptor antagonists, so that one skilled in the art could readily envisage the now claimed genus of CCR5 chemokine receptor antagonists.

Examiner's Rationale No. 3

The Examiner alleged that, although the specification provides a generic assay to identify potential candidate molecules, this assay

fails to lead the skilled artisan to any particular subgenus of inhibitory agents.

Applicants respectfully disagree with the Examiner's characterization of the disclosed assay, i.e, the RET assay. The RET assay does not simply identify *any* chemokine antagonist, instead it specifically identifies CCR5 chemokine receptor antagonists with the properties recited in claim 61. Applicants maintain that the RET assay disclosed is not merely a generic methodology. Based on applicants' disclosure, one skilled in the art can readily perform the disclosed RET screening assay to identify those chemokine antagonists having the properties that are recited in claim 61 and new claim 66. Applicants note that one skilled in the art is also provided with working examples in which this assay was used to identify a number of CCR5 chemokine receptor antagonists with the claimed properties (see, for example, pages 35-36, Table 2a and Table legend).

In addition, applicants note that the specification discloses at page 15, lines 12-24, a second method for identifying CCR5 chemokine receptor antagonists. Specifically, the specification discloses the following assay as a method of identifying CCR5 chemokine receptor antagonists: 1) incubating soluble CD4 with biotinylated gp120 from HIV-1_{JR-FL}; 2) incubating this complex with CCR5-expressing cells that do not express CD4 in the presence or absence of a candidate chemokine antagonist; 3) washing and incubating with streptavidin-phycoerythrin; and 4) washing and measuring the amount of bound gp120 using a flow cytometer or fluorometer; and 5) calculating the degree of inhibition of binding by the candidate chemokines antagonist. Accordingly, applicants maintain that the instant specification provides a written description of CCR5 chemokine receptor antagonists and specific methodology to identify such CCR5 chemokine receptor antagonists that are adequate to establish applicants' possession of the claimed invention.

Examiner's Rationale No. 4

The Examiner alleged that the state of the art as it pertains to HIV

antiviral development is characterized by unpredictability.

In response, applicants respectfully disagree with the Examiner's assessment of the level of skill in the art as it pertains to the claimed invention. Applicants maintain that the level of skill in the art as of the effective filing date was high in the field of biotechnology. At the time of the claimed invention, one skilled in the art could use applicants' disclosure together with general knowledge in the field to readily understand and envisage applicants' invention as recited in claim 61. For example, as the Examiner stated on page 2 of the Office Action, Simmons et al. (1997) disclose a RANTES analogue, aminooxypentane (AOP) RANTES, which potently inhibited macrophage-tropic HIV-1 infection. Although Simmons et al. (1997) is not prior art to applicants' invention, it demonstrates that around the time of the invention, the skill in the art was high, since within a year of applicants' filing date, one skilled in the art isolated a CCR5 chemokine receptor antagonist as recited in the method of claim 61 and new claim 66.

According to the Guidelines For Examination Of Patent Applications Under The 35 U.S.C. 112, ¶1, "Written Description" Requirement, Federal Register Vol. 66, No. 4, p. 1105, Section IIA(2) states that "[g]enerally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement." Accordingly, applicants maintain that the requirements for the disclosure to satisfy the written description requirement where the level of skill in the relevant art is high is less than it would be if the level of skill in the art were low. Thus, one skilled in the art does not require a more specific disclosure than applicants' disclosure.

Finally, applicants note that on page 9 of the February 3, 2006 Office Action previously issued in connection with the subject application, the Examiner acknowledged that the level of skill in the biotechnology art was high at the time of filing.

In view of the foregoing remarks, applicants maintain that the application discloses and describes numerous, exemplary CCR5 chemokine receptor antagonists, as well as methods of particularly identifying more CCR5 chemokine receptor antagonists, and establishes applicants' possession of the invention as recited in claim 61 and new claim 66. Accordingly, applicants maintain that the specification satisfies the written description requirement of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Enablement

The Examiner rejected claim 61 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims. Specifically, the Examiner provided the following five rationales for this ground of rejection. First, the Examiner alleged that the claim breadth potentially encompasses a large genus of poorly defined compounds. Second, the Examiner alleged that the disclosure fails to provide a sufficient number of working embodiments. Third, the disclosure fails to provide sufficient structural guidance pertaining to the molecular determinants modulating CCR5 chemokine receptor antagonist binding to CCR5. Fourth, the Examiner alleged that the disclosure fails to provide sufficient guidance pertaining to those classes of compounds that are capable of inhibiting macrophage-tropic binding interactions. Fifth, the Examiner alleged that it has been well established that the development of suitable HIV-1 therapeutics has been a long and arduous process often ending in failure.

In response, applicants respectfully traverse the Examiner's rejection. Applicants address below each of the Examiner's four rationales for this ground of rejection.

Applicants' Invention

Applicants' invention provides a method of inhibiting infection of a

CD4+ cell by a macrophage-tropic HIV-1 which comprises contacting the CD4+ cell with a CCR5 chemokine receptor antagonist which (a) binds to a CCR5 chemokine receptor on the surface of the CD4+ cell; (b) blocks fusion of HIV-1_{JR-FL} with a PM-1 cell; (c) does not block fusion of HIV-1_{BRU} with such PM-1 cell; and (d) does not activate an inflammatory response upon binding to the CCR5 chemokine receptor on the surface of the CD4+ cell; in an amount and under conditions such that fusion of the macrophage-tropic HIV-1 to the CD4+ cell is inhibited, so as to thereby inhibit infection of the CD4+ cell by the macrophage-tropic HIV-1. In addition, applicants' claimed invention provides that the CCR5 chemokine receptor antagonist may be a polypeptide.

Examiner's Rationale No.1

The Examiner alleged that the claim breadth potentially encompasses a large genus of poorly defined compounds.

In response, applicants maintain that the now claimed genus of CCR5 chemokine receptor antagonists does not encompass all chemokine antagonists, but rather encompasses those which bind specifically to the CCR5 chemokine receptor on the surface of the CD4+ cell; block fusion of HIV-1_{JR-FL} with a PM-1 cell; do not block fusion of HIV-1_{BRU} with such PM-1 cell; and do not activate an inflammatory response upon binding to the CCR5 chemokine receptor on the surface of the CD4+ cell.

In addition, as the Examiner acknowledges on page 6 of the November 16, 2007 Office Action, multiple examples of CCR5 chemokine receptor antagonists are disclosed in the subject application. The specification discloses at page 12, CCR5-specific monoclonal antibodies, namely, 2D7, PA8, PA9, PA10, PA11, and PA12, as chemokine antagonists that inhibit infection of CD4+ cells by HIV-1. In addition, the disclosure beginning on page 26, line 29 and continuing to page 28, line 25, provides polypeptides which are chemokine derivatives that inhibit HIV-1 fusion, including N-terminal derivatives of RANTES, MIP1-α, MIP1-β, such as Met-RANTES, and N-

terminal deletions of RANTES, MIP1-α, MIP1-β or MCP-1, such as the peptide having a deletion of 8 amino acids at the N-terminus of MCP-1. Such polypeptides form an exemplary subgenus of the now claimed genus of CCR5 chemokine receptor antagonists as now recited in new claim 66.

Applicants maintain that the knowledge in the art combined with the disclosure of the subject specification provide a more than adequate written description of the common physical and chemical properties of CCR5 receptor-binding chemokine antagonists, so that one skilled in the art could readily envisage the now claimed genus of CCR5 chemokine receptor antagonists.

Examiner's Rational No. 2

The Examiner alleged that the disclosure fails to provide a sufficient number of working embodiments.

In response, applicants note that, as stated above and disclosed in the application, the CCR5 chemokine receptor antagonist as recited in the claimed method binds to the known CCR5 chemokine receptor for which endogenous chemokine ligands are known in the art in addition to those disclosed in the specification. Specifically, these are disclosed *inter alia* in the specification at page 1, line 32 to page 2, line 3; page 2, lines 28-34; page 7, lines 3-30; Figure 1; page 26, lines 8-18; page 34, lines 33-37; and page 35, Table 2a.

In addition, applicants maintain that one skilled in the art would readily understand a CCR5 chemokine receptor antagonist to be a compound which, upon binding to a chemokine receptor, inhibits or blocks the receptor-mediated response activated by the binding to the receptor of its endogenous ligand(s). Applicants maintain that the binding specificity of the CCR5 chemokine receptor antagonist to the CCR5 chemokine receptor disclosed in the subject application combined with the knowledge in the art regarding antagonists provide sufficient guidance for one skilled in the art to understand the scope of the claimed genus of CCR5 chemokine receptor antagonist.

Examiner's Rationales Nos. 3 and 4

The Examiner alleged that the disclosure fails to provide sufficient structural guidance pertaining to the molecular determinants modulating chemokine antagonist binding to CCR5. The Examiner also alleged that the disclosure fails to provide sufficient guidance pertaining to those classes of compounds that are capable of inhibiting macrophage-tropic binding interactions.

Applicants address the Examiner's third and fourth rationale for this ground of rejection together, because the claimed CCR5 chemokine receptor antagonists are a class of compounds that are capable of specifically inhibiting macrophage-tropic HIV-1 binding interactions as recited in claim 61.

As discussed above, applicants maintain that the description of the CCR5 chemokine receptor antagonists disclosed in the subject application and recited in claim 61, and the knowledge and understanding of one skilled in the art of the properties of a CCR5-receptor binding chemokine antagonist, provide sufficient guidance to one skilled in the art to practice the claimed method without undue experimentation.

Applicants further maintain that the specification discloses, starting on page 36, line 17, that CCR5 is the co-receptor with CD4 needed for HIV-1 entry into a cell. At page 36, lines 20-22, the specification states that "[i]t has been known for a decade that HIV-1 requires a second receptor for entry into CD4+ cells". As stated on page 36, lines 35-37, and as shown on page 37, Table 3, "[t]he expression of C-C CKR-5 on Hela-CD4 (human), COS-CD4 (simian) and 3T3-CD4 (murine) cells rendered each of them readily infectible by the primary, NSI strains ADA and BaL in the env-complementation assay of HIV-1 entry." Accordingly, applicants maintain that the specification discloses that HIV-1 requires two receptors for entry into a CD4+ cell, the second receptor being CCR5, and that the blocking of HIV-1 gp120 binding to CCR5 would inhibit entry of HIV-1 into a CD4+ cell. Thus, applicants maintain that the properties of the CCR5 chemokine receptor

antagonists which enable them to bind to the CCR5 chemokine receptor on the surface of a CD4+ cell, and to block fusion of a CD4+ cell with a macrophage-tropic HIV-1, but not with a T-cell tropic HIV-1, are disclosed in the instant specification. Accordingly, applicants maintain that the specification provides more than adequate guidance pertaining to the nature of the CCR5 chemokine receptor antagonists as recited in the method of claim 61.

Examiner's Rationale No. 5

The Examiner alleged that it has been well established that the development of suitable HIV-1 therapeutics has been a long and arduous process often ending in failure. In support of this assertion, the Examiner cited Oberg and Vrang (1990), Yarchoan and Broder (1992), Gait and Karn (1995), and Flexner and Hendrix (1997).

In response, applicants again respectfully disagree with the Examiner's assessment of the level of skill in the art as it pertains to the claimed invention. Applicants again maintain that the level of skill in the art as of the effective filing date was high in the field of biotechnology, as acknowledged by the Examiner on page 9 of the February 3, 2006 Office Action previously issued in connection with the subject application.

Applicants maintain that as of the effective filing date of this application, one skilled in the art could use applicants' disclosure together with general knowledge in the field to readily understand and envisage applicants' invention as recited in claim 61. For example, as the Examiner stated on page 2 of the Office Action, Simmons et al. (1997) disclose a RANTES analogue, aminooxypentane (AOP) RANTES, which potently inhibited macrophage-tropic HIV-1 infection. Although, Simmons et al. (1997) is not prior art, it demonstrates that around the time of the invention, the skill in the art was high, since within a year of applicants' filing date, one skilled in the art had isolated a CCR5 chemokine receptor antagonists as recited in the method of claim 61 and new claim 66.

In view of the foregoing remarks, applicants maintain that one skilled in the art would have readily been able to make or use applicants' claimed invention based on the subject disclosure supplemented by the knowledge in the art. Accordingly, applicants maintain that the specification satisfies the enablement requirement of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

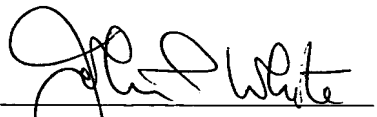
Conclusion

Applicants maintain that in view of the remarks set forth above, the grounds of the Examiner's objections and rejections have been overcome. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these grounds of objections and rejections, and request allowance of pending claims 61 and 66.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $525.00 fee for a three-month extension of time, is deemed necessary in filing this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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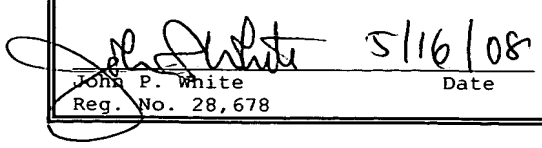
I hereby certify that this correspondence is being deposited on this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



5/16/08
John P. White Date
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